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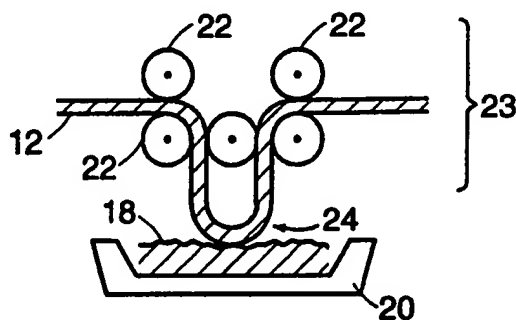


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(54) Title: APPARATUS AND METHODS FOR DROPLET MICROCHEMISTRY**(57) Abstract**

An apparatus and methods for performing microchemical manipulation and analysis of liquid samples. One or more droplets of liquid are loaded serially or in parallel onto a flexible member which may be a fiber or a tape, and are retained on the flexible member by virtue of surface adhesion. Microchemical operations may be performed on these droplets, the operations including mixing, dilution, concentration, heating, cooling, filtering, and analyzing, where the analyzing may include chemical, biochemical, optical, or other physical analyses.



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Apparatus and Methods for Droplet Microchemistry

Technical Field

5 The present invention pertains to an apparatus and methods for transporting a massive number of droplets of liquid and for performing microchemical operations on these droplets, the operations including mixing, dilution, concentration, heating, cooling, filtering, and analyzing, where the analyzing may include chemical, biochemical, optical, or other physical analyses.

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Background of the Invention

Chemistry on the micro-scale, involving the reaction and subsequent analysis of quantities of reagents or analytes of order microliters or smaller, is an increasingly important aspect of the development of new substances in the pharmaceutical and other industries (e.g., synthesis and analysis of new conductive polymers, phosphors, superconductors, etc.). Such reaction and analysis must accommodate vast libraries of compounds to be reacted and analyzed under various conditions. Significant problems associated with current technologies as applied to chemical analysis of vast numbers (potentially on the order of hundreds of thousands or millions per day) of compounds include the problem of conveying analytes from well plates in which libraries of compounds are kept to regions of reaction and analysis, potential contamination of the transport medium, and the sheer size of the facility required to handle vast numbers of compounds and reactions.

Existing technology applies 96-well plates containing quantities on the order of 1 milliliter of liquid compound per well, and, generally, envisions chemical reactions and analysis on flat, two-dimensional surfaces such as silicon chips. In addition to the parallel processing of liquid samples provided by chip technology, a method is required to perform serial steps of liquid sampling, transport, and microchemical analysis.

Summary of the Invention

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In accordance with a preferred embodiment of the invention, there is provided an apparatus for transporting one or more droplets of a liquid. The apparatus has a reservoir for containing a quantity of the liquid and a flexible member for receiving the droplet or droplets of liquid from the reservoir, with the droplets adhering to the flexible

member by virtue of the surface adhesion of the liquid. The flexible member may be a fiber or a ribbon, and a portion of the flexible member may be formed at least temporarily into an enclosure for encapsulating at least one droplet of the liquid.

5 In accordance with a preferred embodiment of another aspect of the present invention, there is provided an apparatus for storing or analyzing a plurality of liquid droplets. The apparatus has a drum having a substantially cylindrical surface and a plurality of wells disposed within the substantially cylindrical surface. The apparatus also has a dispenser for injecting the plurality of droplets into the wells according to a predetermined schedule and may have an analyzer for characterizing at least one
10 chemical property of the droplets. The dispenser may be a flexible transport member wrapped onto the drum in such a manner as to position no more than one droplet of liquid in each well of the drum.

In accordance with other aspects of the present invention, methods are provided for transporting, sampling, mixing, concentrating, diluting, heating, cooling, and
15 analyzing liquid samples by extracting a volume of the liquid by means of the apparatus discussed above. Analysis of physical and chemical properties of the samples may be performed in series or in substantial parallelism.

Brief Description of the Drawings

20 The invention will be more readily understood by reference to the following description, taken with the accompanying drawings, in which:

FIGS. 1A-1C are side views in cross-section of a droplet in adhesion to a fiber in accordance with an embodiment of the present invention;

FIG. 2A is a side view in cross section of a liquid take-up mechanism in
25 accordance with an embodiment of the present invention;

FIGS. 2B-2D show successive steps of liquid take-up onto a fiber in accordance with the embodiment of FIG. 2A;

FIG. 3 depicts the transport of multiple droplets on a fiber, and an advancement mechanism for translating the fiber in accordance with an embodiment of the invention;

30 FIG. 4 depicts the combination of droplets transported to the cite of combination by respective fibers in accordance with an embodiment of the present invention;

FIG. 5 depicts the respective surface areas and volumes of individual and combined droplets borne by a fiber in accordance with an embodiment of the present invention;

FIG. 6 shows the transport and combination of droplets of varying sizes in accordance with an embodiment of the invention;

FIG. 7 is a schematic diagram of a capacitive monitor for sensing the position and characteristics of a microdroplet in accordance with an embodiment of the invention;

FIG. 8 is a plot of the measured capacitance as a droplet traverses the capacitive monitor of Fig. 7;

FIG. 9 is a schematic diagram of a typical optical configuration employed for interrogating a droplet in accordance with an embodiment of the present invention;

FIG. 10 is a perspective view of a sample handling drum for storage and analysis of microsamples conveyed by fiber in accordance with embodiments of the invention;

FIG. 11A is a side view in cross section of a liquid take-up mechanism employing ribbon or tape in accordance with an alternate embodiment of the present invention;

FIGS. 11B-11C show cross-sections of pulleys employed to impart curvature to the ribbon or tape of Fig. 11A; and

FIG. 12 is a perspective view of a ribbon employed in curled and flattened configurations for transport of microdroplets in accordance with embodiments of the invention.

Detailed Description of Preferred Embodiments

Referring first to Fig. 1A, it is recognized that transport, manipulation, and microchemical reaction of materials in the liquid phase or in liquid suspension need not be conducted in a planar environment but may use the adhesion of a droplet 10 to a fiber 12 in order to achieve one or more of the enumerated processes. Processes of adhesion of a liquid to the surface of a solid are discussed, for example, in D. Myers, *Surfaces, Interfaces, and Colloids: Principles and Applications*, (VCH Publishing, NY, 1991), which is incorporated herein by reference. Chapter 17, entitled "Wetting and

Spreading," at pp. 349ff, is of particular relevance.

"Fiber," as used in the present description and in any appended claims, refers to any flexible material the linear dimension of which substantially exceeds the transverse dimensions of the material and includes materials which may be amorphous, such as glass or plastic. It is the geometry rather than the composition of the fiber which is germane to the overall scope of the invention, although the properties of different compositions of fiber may be advantageously exploited, as further described below. The transverse section of the fiber may have any specified shape, thus the fiber may be of circular or elliptical cross section, in the manner of optical fibers, for example. The flexible member may also be flat and ribbon-like, or curled, as discussed below, and references herein to "fiber" are to be understood as also encompassing the generality of flexible members. Materials may include quartz or glass, for example, or amorphous metal (metallic glass), as another example. Metal wires of diameters as small as 25 μm , or even 5 μm , are readily available. Droplet 10 may be referred to herein and in the appended claims as a "microdroplet" or a "sample," and may include droplets containing living cells, such as yeast cells, for example, and may include droplets carrying a single living cell per droplet.

The fiber system described herein for droplet microchemistry may entirely avoid the use of tubes which require cleaning, and may overcome various handling difficulties associated with samples enclosed in conduits. By way of contrast, glass fibers are available at low cost in lengths as long as many kilometers and are readily disposed of after chemical manipulation and analysis are completed.

The following components of a microchemical analysis system are examples of processes which may be carried out through the use of fiber technology in accordance with various embodiments of the present invention:

1. Sampling - i.e., transferring a small amount of a specified fluid to a fiber from either a reservoir of fluid or another surface;
2. Transporting fluid samples;
3. Adding one sample to another;
4. Diluting a sample;
5. Concentrating a sample;
6. Heating or Cooling a sample;

7. Extracting or filtering chemicals contained within a sample;
8. Analyzing chemicals as to their composition or other chemical or physical characteristics.

The quantity of fluid adhering to fiber 12 and thus constituting droplet 10 is a function of the respective compositions of fiber 12 and droplet 10 and of the method in which adhesion of the droplet to the fiber is attained. In practice, variations in volume of over a factor of 1000 have been achieved. The surface tension of droplet 10, for example, serves to counter unlimited diffusion of the fluid along the length of the fiber. Where fiber 12 is not wetted by droplet 10, tangent 16 to outer surface 14 of droplet 10 forms contact angle 18 with the local surface of fiber 12. Where wetting of fiber 12 by droplet 10 occurs, as shown in Fig. 1B, the spread of droplet 10 along fiber 12 is limited by surface tension. The size of the droplet is related to the transverse dimension (or dimensions) of the fiber; for example, a fiber of 100 μm diameter may hold a droplet of over five times that diameter.

For transportation of droplet 10, it is preferred that droplet 10 surround fiber 12, as shown in Fig. 1C.

Sampling of materials in liquid form, thereby loading the fiber, is now described with reference to Fig. 2. Fiber 12 may be guided, by any mechanical arrangement known in the mechanical arts, so as to come in contact with liquid 18 which may be contained within reservoir 20. Quartz is a preferred material for fiber 12 as it is very strong. Fiber 12 may be guided, for example, by means of pulleys 22, comprising pulley feed mechanism 23, so as to form loop 24. Loop 24 is brought in a direction designated by arrow 26 into contact with liquid 18, as shown in Fig. 2B, preferably without penetrating the surface of the liquid. As loop 24 is withdrawn in direction 28 away from the surface of the liquid, as shown in FIG. 2C, droplet 10 begins to form on fiber 12. As loop 24 is withdrawn further, droplet 10 detaches from liquid reservoir 20, as shown in FIG. 2D.

The rate at which fiber 12 is withdrawn from liquid reservoir 20 contributes to determining the size of droplet 10 that is formed, with a slower withdrawal resulting in a smaller droplet. Higher velocities result in larger droplets, whereas higher velocities yet result in loss of the droplet to dripping back into the reservoir. Pulley feed

mechanism 23 also serves to impel fiber 12 in the direction of its longitudinal axis.

A typical volume of fluid sampled by a fiber in the manner described is of the following order: assuming a sphere of fluid having a diameter of 300 μm surrounding a fiber of 100 μm diameter, and removing the volume displaced by the presence of the fiber, the volume of the liquid droplet is on the order of 12 nanoliters. Since the volume of the droplet scales substantially as the cube of the characteristic transverse dimension of the fiber, a fiber of 1 mm diameter may be used to transport droplets of volume on the order of 10 microliters. In fact, droplet volumes between 10 picoliters and 10 microliters are readily handled in accordance with the invention.

Referring, once more, to Fig. 2A, contact between fiber 12 and the liquid in reservoir 20 may be achieved in any of a variety of ways. In accordance with a preferred embodiment of the invention, reservoir 20 may be raised so that surface 26 of liquid 18 makes contact with fiber loop 24. Alternatively, the entire pulley feed mechanism 23 may be lowered to that loop 24 makes contact with liquid 18, or, in accordance with another embodiment, the speed of rotation of pulleys 22 may be differentially governed to regulate the length of loop 24. It is to be understood that additional pulleys may be provided within the scope of the invention, such as to provide for differential advancement of the leading and trailing knees of loop 24.

Transportation

A fiber, as described, may hold a large number of liquid droplets and convey all the droplets in a specified direction for serial handling on a massive scale. Referring now to Fig. 3 and considering fiber 12 to have a diameter of 100 μm , for example, droplets 10 may be conveyed with an inter-droplet spacing 30 of 500 μm or less. Thus, over 2000 droplets may be loaded per meter of fiber, and 500 m of fiber can hold and transport over one million droplets, where the composition of the individual droplets may vary.

Additionally, in accordance with a further embodiment of the invention, small solid particles 31 may be held to fiber 12 by electrostatic attraction or by forces of liquid surface adhesion and similarly transported, manipulated and analyzed by the disclosed system. In order for fiber 12 to be advanced by pulleys 22, provision must be made not to interfere with the conveyance of droplets 10. One method of providing for fiber

advancement is to provide radial members 32 that contact fiber 12 only at positions 34 where no droplets are present. Pulleys 22 are shown in this figure to be counterrotating so as to advance fiber 12 in direction 36, to the right in this figure.

5 In an alternate embodiment of the invention, the fiber may be magnetized at specified locations or intervals and a magnetically attractable bead may be attracted at those locations and surrounded by the liquid to be transported.

Once droplets 10 have been loaded onto fiber 12, they may be heated or cooled, and functions of microchemistry and analysis may be performed on them, as discussed in greater detail in the following discussion.

10 **Addition of chemicals via fiber technology**

Referring now to Fig. 4, distinct droplets, of the same or different chemical composition, may be combined using the droplet microchemistry methods of the present invention. a first fiber 40, carrying droplets 42 may be moved with respect to a second fiber 44 carrying other droplets 46 such that fibers 40 and 44 lie in substantially locally parallel planes and have a specified relative angle 48 which may be a right angle. When fiber 40 is brought within sufficient proximity of fiber 44, a single droplet 49 may be formed by the combination of droplets from each of fibers 40 and 44. When fiber 40 is now moved away from fiber 44, combined droplet 49 tends to move to one or the other of fibers 40 and 44. In order to select which fiber will receive combined droplet 49, one fiber, say, for example, fiber 44, may be moved substantially transversely to the other fiber, and then the fibers are separated. The fibers are distinguished in this way since the force required to move a droplet along a fiber differs from the force required to remove the droplet from the fiber or to impart momentum to the liquid in a direction tangential to the circumference of the fiber.

25 In the manner described, thousands of droplets conveyed by a single fiber may be combined with thousands of droplets conveyed by a second fiber by sequentially bringing the droplets into mutual contact.

In Fig. 5, the surface areas and volumes of two droplets 50, assumed to be equal, are compared with the same quantities of combined droplet 52 which results from the combination of the original droplets 50 in accordance with the preceding discussion. While the volume of fluid of droplet 52 is twice that of either droplet 50, the surface

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area of droplet 52 is less than twice that of either droplet 50. Since the surface area of droplet 52, and thus its surface energy which increases with surface area, is less than the sum of the corresponding quantities for the separate droplets, the combination configuration is energetically favored.

5 As shown in Fig. 6, droplets 42 transported by fiber 40 in axial direction 36 may be of a different size or volume from droplets 46 transported by fiber 44 prior to their combination with droplets 44 to produce combined droplets 49. In fact, within the scope of the invention, there is no restriction on the sizes of particular droplets. Since the chemical composition of the various droplets is controlled, a computer may track them
10 all and control the chemical reactions taking place among the droplets.

Probes of droplet position and physical characteristics

Capacitive

Variability in droplet position with reference to laboratory-fixed instrumentation may arise because of lengthening or shortening of the fiber due, in turn, to thermal
15 expansion or tensile stress, for example. In order to track the droplet position with great precision, several methods may be practiced. Referring to Fig. 7, a capacitance sensor, designated generally by numeral 70, is used to measure the capacitance between plates 72. a capacitance meter 74, such as known in the art, is connected across the plates and supplies an output signal characterizing the capacitance. The clearance between plates
20 72 must be sufficient to provide clearance for fiber 12 and droplet 10, while the width of plates 72 must be no longer than to allow clear resolution of individual droplets. Depending on the dielectric properties of a given droplet 10, the capacitance measured across plates 72 increases or decreases as droplet 10 enters the region between the plates, as fiber 12 advances in direction 36. The plot 80 in Fig. 8 depicts the
25 capacitance, plotted along the vertical axis, as a function of the displacement x of fiber 12. The width w of the capacitance feature corresponds, substantially, to the width of the droplet convolved with the width of plates 72, and may be dominated by the width of the plates if it significantly exceeds the width of the droplet. Using this technique, the mid-droplet position 82 is accurately determined.

30 Plot 80 of capacitance as a function of fiber position also allows other parameters to be determined. For example, the integral of curve 80 is proportional to the

volume of the droplet for a given plate geometry and dielectric constant of the liquid. By making the plate length shorter than the droplet length, the width of the curve yields the droplet length directly, and, otherwise, the droplet width may be derived by deconvolution of the known plate width. Similarly, the dielectric constant of the liquid and the known dielectric properties and geometry of the fiber allow the volume to be derived given an absolute measurement of incremental change in capacitance as the droplet passes through the plates.

Similarly, once the droplet volume and length are known, the diameter is readily calculated.

Alternatively, if the volume of the droplet is derived by independent means such as by one of the optical methods described below, the capacitance technique described may be used to infer the dielectric constant of the droplet and thus aspects of its material/chemical characteristics.

Optical

Referring now to Fig. 9, other methods for interrogating the physical and chemical properties of droplet 10 conveyed in direction 36 by fiber 12 employ a microscope designated generally by numeral 90. The optical arrangement may be confocal (of Type I or Type II) with the interrogated droplet 10 and an aperture stop 92 at conjugate foci of the system, or otherwise, using any optical arrangement known to persons skilled in the optical arts. Using any such arrangement, a source of illumination 94, which may be a broadband source of light or a monochromatic source such as a laser, provides a light beam 96 that is collimated by collimating optics 98. In accordance with a preferred embodiment of the invention, beam 96 is focused by focussing optics 100 to form a focus in the vicinity of droplet 10. A fraction of the light reflected from droplet 10 is deflected by beam-splitter 102 and focussed onto photodetector 104.

As droplet 10 traverses beam 96, the intensity of reflected light measured at photodetector 104 varies, with optimal performance achieved when aperture stop 92 is matched to the size of droplet 10. As discussed above, an optical technique may be employed to derived droplet size, whereupon the capacitive technique yields information relating to the dielectric properties of the individual droplets.

In accordance with further embodiments of the invention, the light returned from the droplet, whether by reflection or scattering, may be spectrally analyzed, using any or all spectroscopic techniques known in the spectroscopic arts, to derive information regarding the composition and physical state of the liquid comprising droplet 10. These techniques include fluorescence detection systems based on the fluorescent response, for example, to target drug/protein interactions.

Additionally, microscope arrangement 90 may be employed to create an image of droplet 10 at the focal plane where aperture stop 92 is shown. Placing a camera array, such as a CCD array, in the focal plane allows an image signal to be derived, according to standard optical techniques.

Longitudinal propulsion of droplets along the fiber

In addition to conveyance of the droplets by moving the underlying fiber, one or more droplets may be moved relative to the fiber. In accordance with one technique for moving a droplet, optical tweezers are employed, using the known effect of dipole forces created by the scattering of light as it passes through a diffractive interface between two dielectric media such as the ambient air and the droplet. The light beam is applied by focussing a laser beam to a confocal zone of the same dimension as the droplet such that the droplet is constrained to remain within the waist of the beam.

In accordance with an alternate embodiment of the invention, acoustic pulses are launched from opposite ends of the droplet-laden fiber by means of acoustic transducers such as piezo actuators. The two pulses are designed such that they collide to create an asymmetric longitudinal pulse tending to urge the fiber and thus the droplet preferentially in one direction along the axial length of the fiber. This forms a type of "inertial stepping" as is known in the art of tunneling microscopy for moving solid objects. Using this technique, particular droplets along the fiber may be addressed.

Various embodiments of the invention, as described above, may be advantageously employed for sampling droplets from a 96-well plate such as is used extensively in areas of biology, pharmacology, etc. A single fiber may be used for sequentially sampling droplets from each of the 96 wells on the plate. In accordance with an alternative embodiment of the invention, a sampling assembly, such as depicted in Fig. 2A, provides for simultaneous sampling of a plurality of wells by means of a

plurality of loops, either of the same fiber or of various fibers. This provides for rapid sampling and conveyance of large numbers of microdroplets, of as many as 96,000 droplets sampled from 1000 plates in the course of on the order of 1.5 hours.

Fiber Storage and Analysis

5 Referring now to Fig. 10, a retaining drum 100 is shown which may serve one or more of the following three functions: a) retaining the droplet-laden fiber 12 in such a manner as not to perturb the integrity of the droplets; b) pulling fiber 12 for conveyance of droplets 10 suspended therefrom; and c) providing a platform for analysis, in massive parallelism if required, of suspended droplets 10.

10 Drum 100 is rotated about its axis 102 by means of a motor (not shown) driving shaft 104, via any appropriate mechanical coupling. Drum retains fiber 12 in spiral groove 106 which has a pitch equal to the fiber turn-to-turn spacing when the fiber is wound on the drum. Fiber 12 may be taken up or unwound from either end, as shown. In a preferred embodiment, fiber 12 is continuously taken up and paid out, possibly to a
15 further drum for subsequent analysis or to a spool for disposal. A typical pitch may be 500 μm . For an interdroplet spacing of 500 μm , a drum of 100-mm circumference holds 200 samples per revolution, and, with a 500- μm pitch, 10^5 samples per 250-mm length of drum may be retained for storage or analysis. Groove 106 has indentations, holes, or depressions (wells) at the droplet spacing so that the droplets are not perturbed by
20 winding of fiber 12 on drum 100. These holes may be employed for optical transmission between the interior and exterior of the drum to facilitate optical analysis by means of a detector addressing individual droplets, serially or in parallel by means of a detector array. In a preferred embodiment, a stepping motor is employed for rotating the drum, the motor having 100,000 steps per revolution for accurate registration of the drum
25 position. Such a motor provides 1- μm positioning capability with respect to the fiber wound on the drum.

It is to be understood that samples 10 may either be retained in adhesion to fiber 12 while wound on drum 100, or, alternatively, samples 10 may be deposited, in whole or in portion, on drum 100 using fiber 12 for dispensing the droplets onto the drum,
30 whereupon fiber 12 may be removed.

Ribbon Transport

Referring now to Figs. 11A-C, an alternate embodiment of the invention employs a flexible transport member for transportation of droplets where the flexible transport member is a tape or ribbon **110**, as shown in cross-section in Fig. 11A. Tape **110** may be glass, quartz, metal, or various other materials. Amorphous metal (metallic glass) ribbon is preferred since it can sustain tight radii of bending and additionally has a very high tensile strength. These properties are advantage for high-rate sampling, using a loop feed mechanism having pulleys **A₁**, **B₁**, **A₂**, and **B₂** as shown. As described with reference to Fig. 2A, flexible member **110** is brought into contact with surface **112** of liquid **114** and droplets adhere to the flexible member. In certain embodiments of the invention, it is desirable to impart a curvature to ribbon **110**. This is achieved by providing respectively convex and concave curved circumferential surfaces **116** and **118** shown in Fig. 11B and 11C, where pulleys **A** and **B** are shown in cross-section. The concave surface **118** may also serve as a recess for straddling liquid droplets borne by the flexible member.

Alternatively, as shown in Fig. 12, ribbon **110** may be fully curled in its entirety or in segments, such as to have flat segments **120** and fully curled segments **122**. Full curling forms a cylinder which may be employed advantageously to encapsulate liquid droplet **10**, thereby minimizing or eliminating evaporation of material from droplet **10** during any latency period required in processing the droplet. Ribbon **110** may subsequently be uncurled to provide ready access to liquid droplet **10**.

The described embodiments of the invention are intended to be merely exemplary and numerous variations and modifications will be apparent to those skilled in the art. All such variations and modifications are intended to be within the scope of the present invention as defined in the appended claims.

I CLAIM:

1. An apparatus for transporting at least one droplet of a liquid having a surface tension, the apparatus comprising:
 - a. a reservoir for containing a quantity of the liquid;
 - 5 b. a flexible member disposed for receiving the at least one droplet of the liquid from the reservoir, the at least one droplet of the liquid adhering to the flexible member by virtue of the surface tension of the liquid.
2. An apparatus according to claim 1, wherein the flexible member is a fiber.
3. An apparatus according to claim 1, wherein the flexible member has a
10 characteristic cross-sectional dimension smaller than 100 micrometers.
4. An apparatus according to claim 1, wherein the flexible member is a ribbon.
5. An apparatus according to claim 1, wherein a portion up to the whole of the flexible member is formed at least temporarily into an enclosure for encapsulating at least one droplet of the liquid.
- 15 6. An apparatus according to claim 1, wherein the flexible member is composed of an amorphous material.
7. An apparatus according to claim 5, wherein the amorphous material is glass.
8. An apparatus according to claim 5, wherein the amorphous material is metal.
9. An apparatus according to claim 1, further comprising an impeller for urging the
20 flexible member in at least one direction.
10. An apparatus according to claim 8, wherein the impeller comprises at least one pulley for imparting motion to the flexible member.
11. An apparatus according to claim 9, wherein the at least one pulley includes a circumferential recess for straddling the at least one droplet of liquid during motion of
25 the flexible member.
12. An apparatus according to claim 1, further comprising a mounting arrangement permitting bending of the flexible member while in motion.
13. An apparatus for analyzing a plurality of liquid droplets, the apparatus comprising:
 - 30 a. a drum having a substantially cylindrical surface;
 - b. a plurality of wells disposed within the substantially cylindrical surface

of the drum;

- c. a dispenser for injecting the plurality of droplets into the plurality of wells according to a predetermined schedule; and
- d. an analyzer for characterizing at least one chemical property of the plurality of droplets.

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14. An apparatus according to claim 12, wherein the dispenser comprises a flexible transport member wrapped onto the drum in such a manner as to position no more than one droplet of liquid in each well of the drum.

15. An apparatus for storing a plurality of liquid droplets, the apparatus comprising:

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- a. a drum having a substantially cylindrical surface;
- b. a plurality of wells disposed within the substantially cylindrical surface of the drum;
- c. a dispenser for injecting the plurality of droplets into the plurality of wells according to a predetermined schedule.

15

16. A method for transporting a liquid having a surface tension, the method comprising:

- a. providing a flexible member capable of motion in at least one direction;
- b. adhering at least one droplet of the liquid to the flexible member by virtue of the surface tension of the liquid; and
- c. moving the flexible member in the at least one direction.

20

17. A method for sampling a liquid having a surface and a surface tension, the method comprising:

- a. providing a flexible member capable of motion in at least one direction;
- b. bringing a portion of the flexible member into momentary contact with the surface of the liquid; and
- c. translating the flexible member in a direction having a component normal to the surface of the liquid.

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18. A method for optically analyzing a liquid having a surface and a surface tension, the method comprising:

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- a. providing a flexible member having a longitudinal orientation;
- b. adhering a droplet of the liquid to the flexible member by virtue of the

surface tension of the liquid; and

- c. positioning the droplet within the focal region of an optical probe having an optical axis.

5 **19.** A method according to claim 17, wherein the step of positioning includes aligning the longitudinal orientation of the flexible member along the optical axis for maximizing optical sampling of the droplet.

10 **20.** A method for conducting microchemistry, the method comprising:
a. extracting a volume of liquid substantially smaller than one microliter;
b. performing at least one operation on the volume of liquid chosen from the group of operations including filtering, diluting, concentrating, heating, cooling, filtering, and analyzing.

15 **21.** A method according to claim 20, wherein the step of extracting comprises:
a. providing a flexible member having a longitudinal orientation; and
b. adhering a droplet of the liquid to the flexible member by virtue of the surface tension of the liquid.

20 **22.** A method for filtering a liquid having a surface tension, the method comprising:
a. providing a flexible member having a surface having a compound-selective wetting characteristic;
b. bringing a portion of the flexible member into momentary contact with the surface of the liquid; and
c. adhering a droplet of the liquid preferentially containing a desired compound to the flexible member by virtue of the surface tension of the liquid and the compound-selective wetting characteristic of the flexible member.

25 **23.** A method for translating a droplet of liquid adhering to a flexible member at a predetermined position on the flexible member by virtue of the surface tension of the fluid, the method comprising:
a. launching a first impulse on the flexible member, the first impulse having a first amplitude, the first impulse traveling from a first direction past the predetermined position of the droplet on the flexible member;
30 and

- 5 b. simultaneously launching a second impulse on the flexible member, the second impulse having a second amplitude unequal to the first amplitude of the first impulse, the second impulse traveling from a direction counter to the first direction past the predetermined position of the droplet on the flexible member.

24. A method for translating a droplet of liquid adhering to a flexible member at a predetermined position on the flexible member, the method comprising:

- a. focusing a laser at the predetermined position on the flexible member;
 and
10 b. applying an optical impulse for imparting momentum to the droplet in a desired direction.

25. A method of mixing a first and second liquid, both liquids having surface tension, the method comprising:

- a. providing a first flexible member having a longitudinal orientation;
15 b. adhering a first droplet of the first liquid to the first flexible member by virtue of the surface tension of the first liquid;
 c. providing a second flexible member having a direction of motion disposed substantially perpendicular to the longitudinal orientation of the first flexible member;
20 d. adhering a second droplet of the second liquid to the second flexible member by virtue of the surface tension of the second liquid;
 e. bringing the first droplet into contact with the second droplet during the course of relative motion of the first and second flexible members.

26. A method for measuring the position and dielectric properties of a droplet of liquid adhering to a flexible member at a position on the flexible member, the method comprising:

- a. creating an electric field in a region of space characterizing the capacitance between two conductors;
 b. passing the position of adhesion of the droplet on the flexible member
30 through the region containing the electric field;
 c. measuring the capacitance between the two conductors at a specified frequency; and

- d. characterizing dielectric properties of the droplet as a function of time based on the measured capacitance.
27. A method for transporting a solid particle, the method comprising:
- a. providing a flexible member capable of motion in at least one direction;
 - 5 b. adhering the solid particle to the flexible member by virtue of electrostatic force between the particle and the flexible member; and
 - c. moving the flexible member in the at least one direction.

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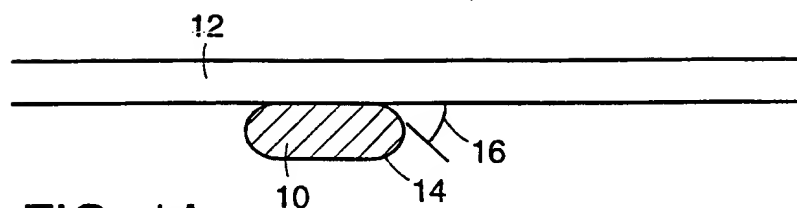


FIG. 1A

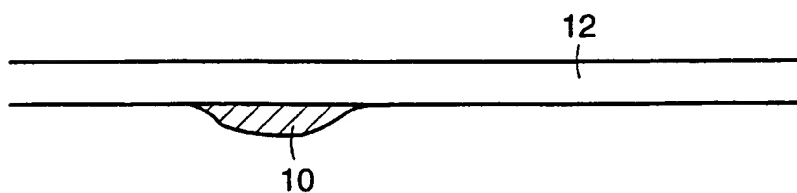


FIG. 1B

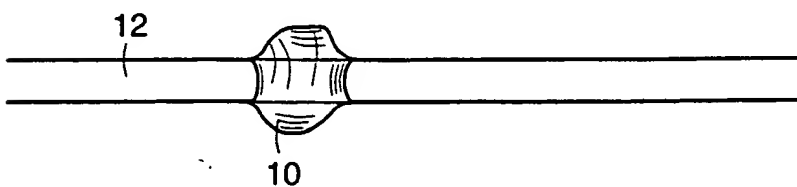


FIG. 1C

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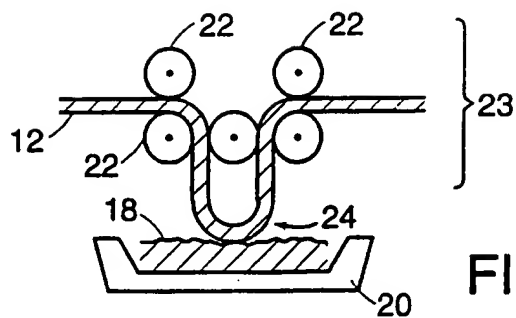


FIG. 2A

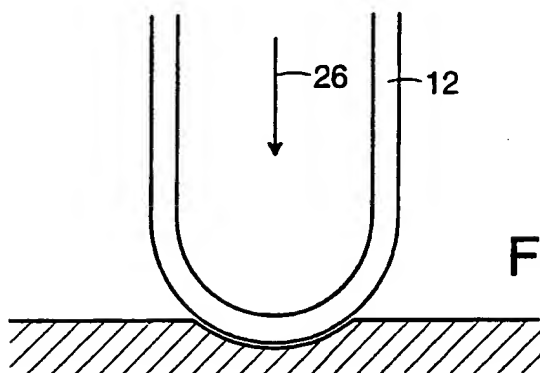


FIG. 2B

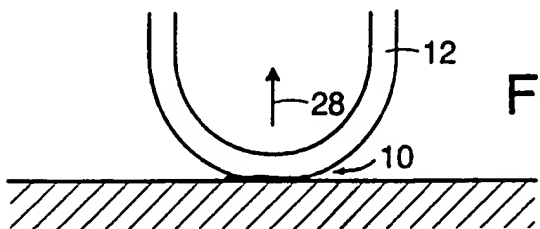


FIG. 2C

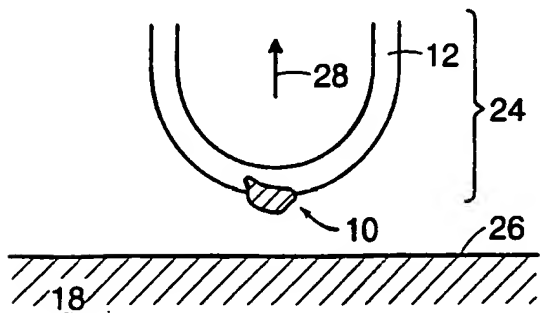


FIG. 2D

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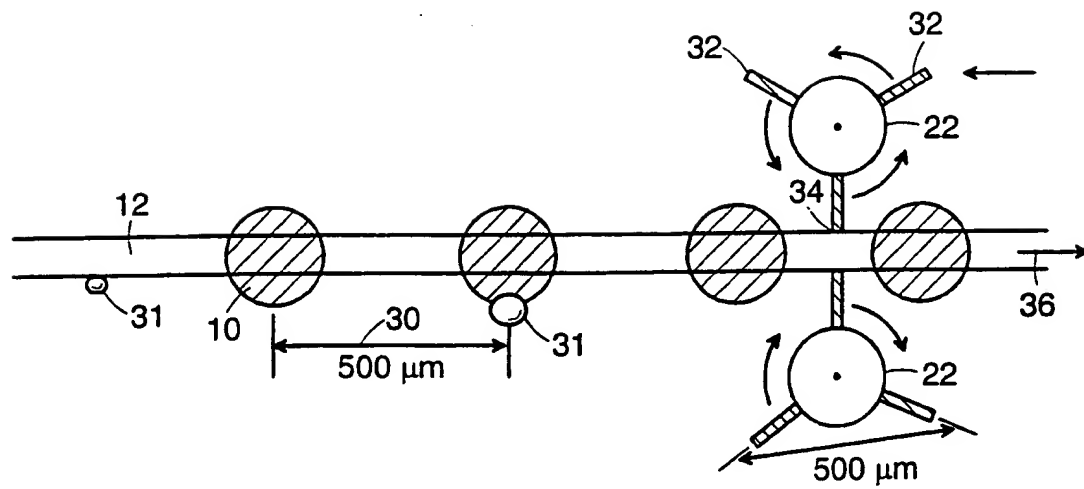


FIG. 3

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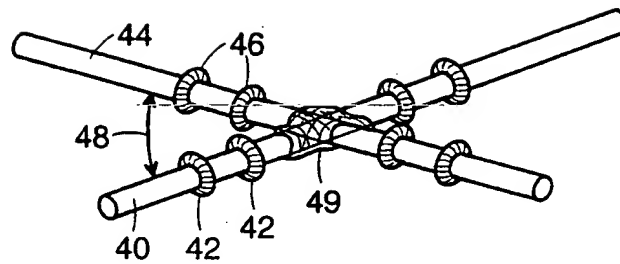


FIG. 4

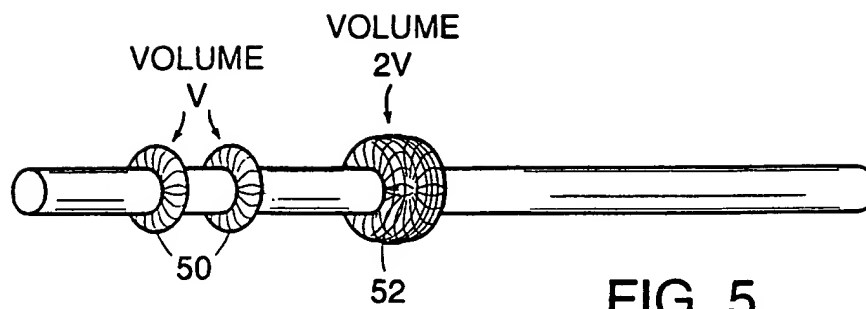


FIG. 5

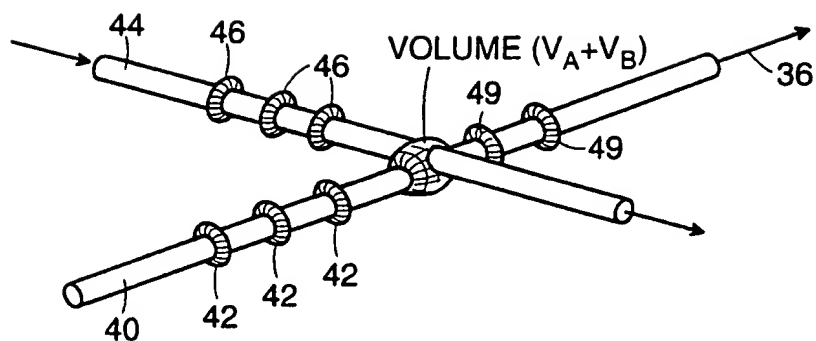


FIG. 6

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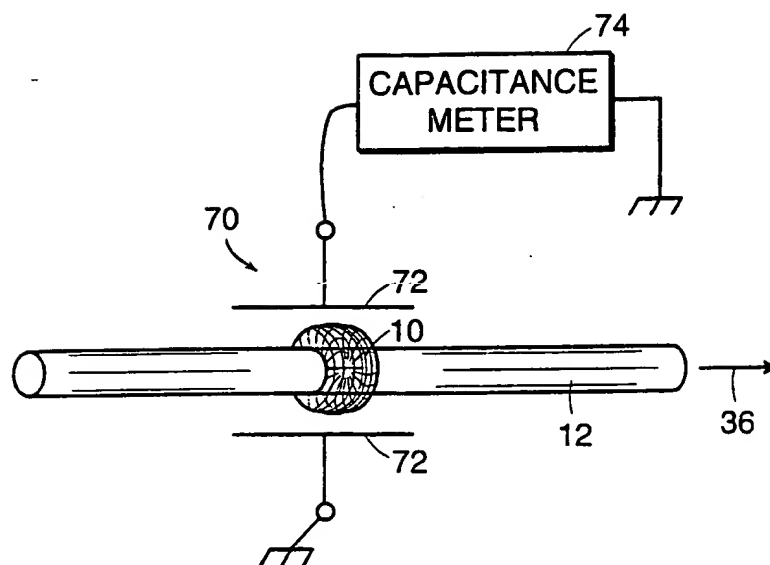


FIG. 7

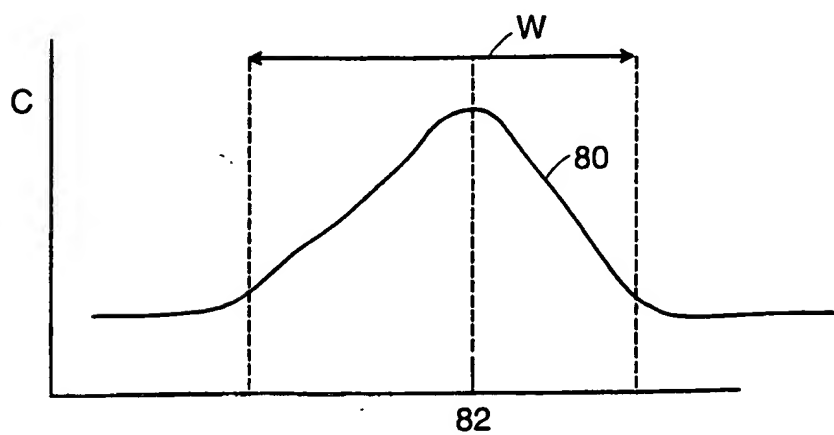


FIG. 8

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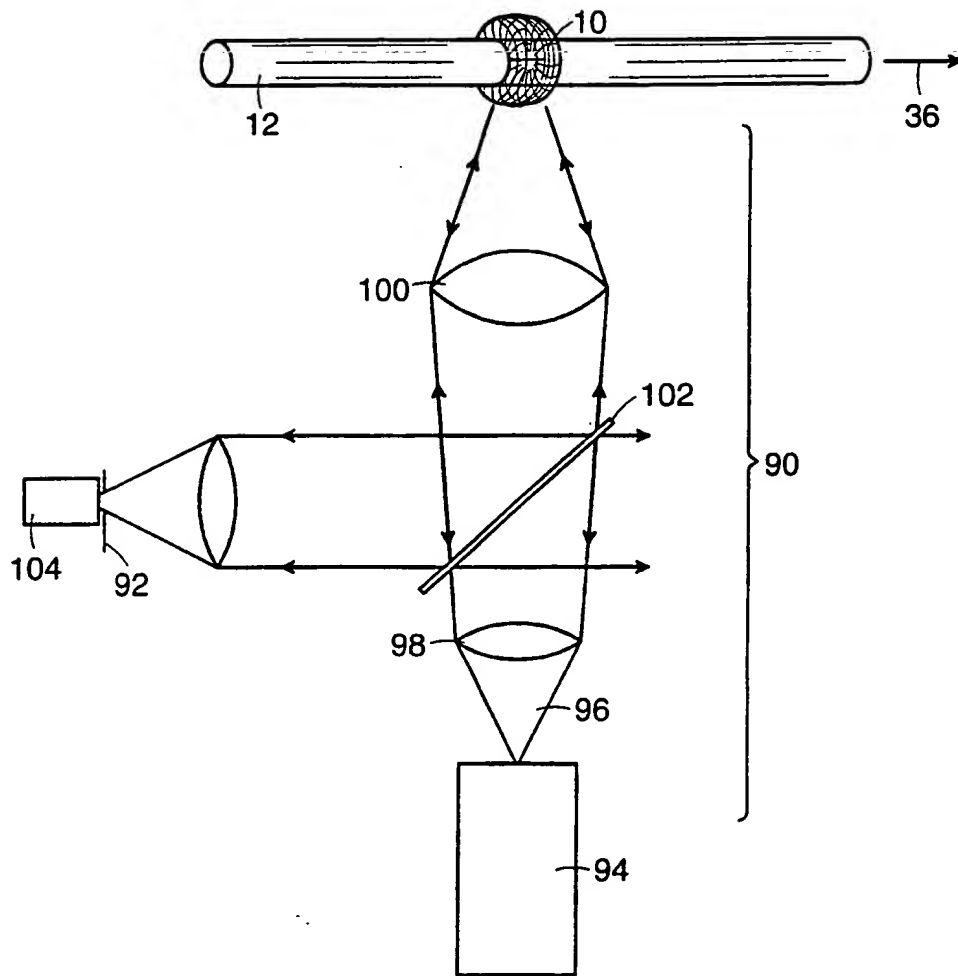


FIG. 9

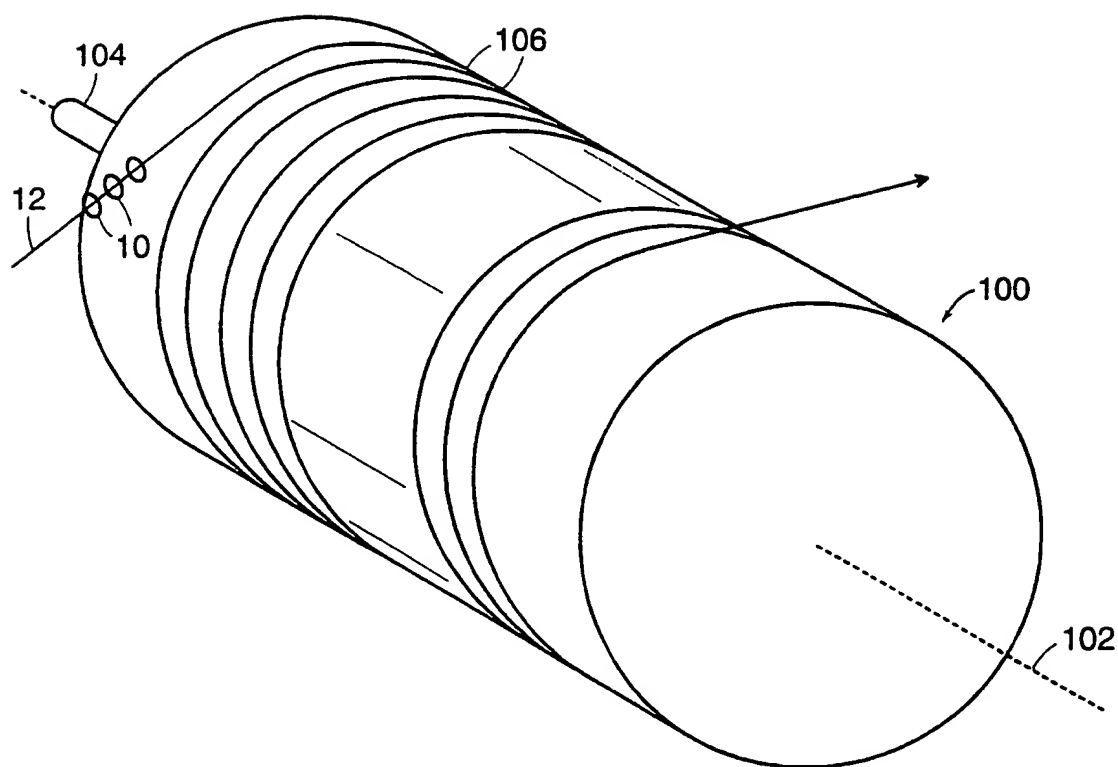


FIG. 10

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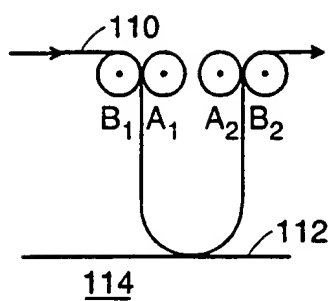


FIG. 11A

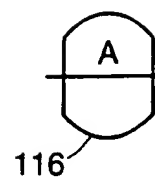


FIG. 11B

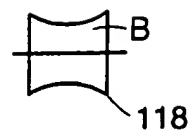


FIG. 11C

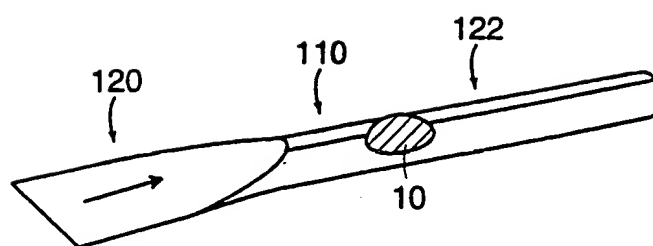
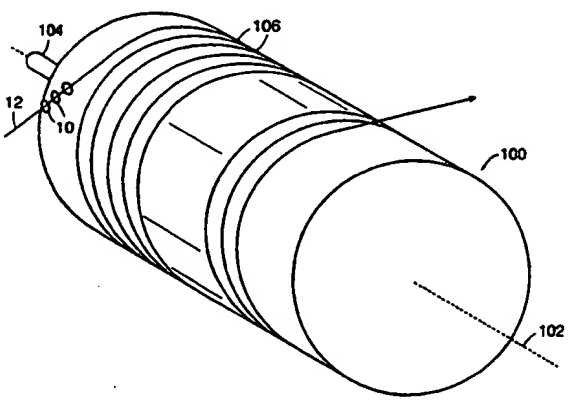


FIG. 12

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶: B01L 3/02, G01N 35/02, B01L 3/00, H05H 3/04, G01D 5/24, B01F 15/00, B01J 4/02	A3	(11) International Publication Number: WO 99/11373 (43) International Publication Date: 11 March 1999 (11.03.99)
(21) International Application Number: PCT/US98/17306 (22) International Filing Date: 20 August 1998 (20.08.98) (30) Priority Data: 60/057,734 28 August 1997 (28.08.97) US (71)(72) Applicant and Inventor: HUNTER, Ian, W. [US/US]; 6 Oakdale Lane, Lincoln, MA 01773 (US). (74) Agents: SUNSTEIN, Bruce, D. et al.; Bromberg & Sunstein LLP, 125 Summer Street, Boston, MA 02110-1618 (US).	(81) Designated States: CA, JP, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published <i>With international search report.</i> (88) Date of publication of the international search report: 29 July 1999 (29.07.99)	
(54) Title: APPARATUS AND METHODS FOR DROPLET MICROCHEMISTRY (57) Abstract <p>An apparatus and methods for performing microchemical manipulation and analysis of liquid samples. One or more droplets of liquid are loaded serially or in parallel onto a flexible member which may be a fiber or a tape, and are retained on the flexible member by virtue of surface adhesion. Microchemical operations may be performed on these droplets, the operations including mixing, dilution, concentration, heating, cooling, filtering, and analyzing, where the analyzing may include chemical, biochemical, optical, or other physical analyses.</p> 		

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/17306

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 B01L3/02 G01N35/02 B01L3/00 H05H3/04 G01D5/24
B01F15/00 B01J4/02

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 B01L G01N G01D H05H

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 3 566 677 A (COLE BENJAMIN T ET AL) 2 March 1971 see column 6, line 37 - line 45; figure 5 see column 4, line 52 - line 68 see column 3, line 1 - line 23; figure 1 ---	1,6, 8-10,16, 17
X	EP 0 641 599 A (BOEHRINGER MANNHEIM GMBH) 8 March 1995 see page 2, line 18 - line 32 see page 6, line 30 - line 43; figures --- -/--	1,2, 16-18, 20,21



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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Date of the actual completion of the international search

20 April 1999

Date of mailing of the international search report

28.05.99

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/17306

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 334 837 A (IKEDA MASAHIKO ET AL) 2 August 1994 see column 15, line 1 - line 10; figure 19 see column 15, line 38 - line 59; figures 21,22 see column 17, line 30 - column 18, line 34; figures 26-29 ---	1,4
P,X	WO 98 15355 A (DANNOUX THIERRY L A ;CORNING INC (US)) 16 April 1998 see page 3, line 3 - line 18; claims 1,13,15; figures ---	1,2,16, 17
A	DD 247 857 A (PAEDAGOGISCHE HOCHSCHULE KARL) 22 July 1987 see the whole document ---	1
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A	US 4 841 145 A (WADA AKIO ET AL) 20 June 1989 see column 7, line 25 - line 46; figure 9 see column 6, line 38 - line 66; figure 6 see column 4, line 61 - line 65 see column 4, line 19 - line 29 ---	1,4,6,8, 10,16
A	see column 4, line 19 - line 29 ---	5
X	US 3 734 622 A (ADLER S) 22 May 1973 see column 6, line 3 - line 18; figure 4 ---	1,18
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A	see column 6, line 3 - line 13 ---	5
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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/17306

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 3 855 846 A (FORGET R ET AL) 24 December 1974	1
A	see column 1, line 10 - line 14	1
Y	see column 1, line 49 - line 64	
Y	see column 3, line 1 - line 21	22
Y	WO 83 03677 A (GENEFUSION SA) 27 October 1983 see page 3, line 3 - page 4, line 29; claim 1; figures see page 8, line 2 - line 6	22
A	US 5 006 749 A (WHITE RICHARD M) 9 April 1991 see column 2, line 6 - line 9	23
A	see column 7, line 67 - column 8, line 5	
A	see column 8, line 14 - line 20	
A	see column 10, line 48 - line 54	26
A	see column 12, line 7 - line 21	
A	PATENT ABSTRACTS OF JAPAN vol. 009, no. 140 (E-321), 14 June 1985 & JP 60 022478 A (SHINSEI KOGYO:KK), 4 February 1985 see abstract	23
A	US 5 486 337 A (OHKAWA TIHIRO) 23 January 1996 see column 2, line 26 - line 61; claims 1,3,4,7; figures	23,25
A	US 3 710 279 A (ASHKIN A) 9 January 1973 see column 1, line 25 - line 32 see column 5, line 8 - line 23 see column 5, line 54 - column 6, line 17	24
A	EP 0 556 748 A (CANON KK) 25 August 1993 see column 1, line 34 - line 49 see column 8, line 24 - line 44; figure 5	24
A	US 4 659 677 A (GLOVER, CLYDE P ET AL) 21 April 1987 see column 3, line 13 - line 23; claims 1,3; figures 8A-8E,9 see column 5, line 5 - column 6, line 21	25
A	WO 95 34374 A (BEHRINGWERKE AG) 21 December 1995 see page 18, line 9 - line 17; claims 6,7,9-11,14,15,19-21; figures	25

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INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 98/17306

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 643 628 A (SONDEREGGER MARCEL) 1 July 1997 see column 3, line 16 - line 18 see column 7, line 6 - line 27 see column 8, line 49 - column 9, line 17; figure 10 ---	1,25
X	EP 0 286 419 A (MCMILLAN NORMAN) 12 October 1988 see column 2, line 11 - line 16; figures see column 4, line 18 - line 27 see column 5, line 50 - column 6, line 4; figure 6 ---	1,2,6,7, 16,17,19
A	see column 6, line 49 - line 60 ---	26
A	US 4 568 875 A (PISO JOHN S ET AL) 4 February 1986 see column 2, line 15 - line 41 ---	26
A	US 4 196 615 A (DAVIS BRUCE W) 8 April 1980 see column 4, line 43 - line 61; figure 1 see column 6, line 17 - line 33 ---	26
X	DE 23 07 075 A (HAUNI WERKE KOERBER & CO KG) 22 August 1974 see page 6, line 5 - line 21; figure ---	27
X	EP 0 752 281 A (PROTEC SRL) 8 January 1997 see column 3, line 41 - column 4, line 7 see column 7, line 4 - line 23 -----	27

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 98/ 17306

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a)

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

- | | |
|------------------|---------------|
| 1. CLAIMS: 1-21 | 2. CLAIMS: 22 |
| 3. CLAIMS: 23-24 | 4. CLAIMS: 25 |
| 5. CLAIMS: 26 | 6. CLAIMS: 27 |

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1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☒ No protest accompanied the payment of additional search fees.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1-21

apparatus for sampling and transporting at least a droplet adhering to a flexible member by virtue of the surface tension of the liquid

2. Claim : 22

method for filtering a liquid comprising adhering a droplet of the liquid preferentially containing a desired compound to a flexible member

3. Claims: 23-24

methods for translating a droplet adhering to a flexible member

4. Claim : 25

method for mixing a first and a second droplets adhering to a flexible member.

5. Claim : 26

method for measuring the position and dielectric properties of a droplet adhering to a flexible member.

6. Claim : 27

method for transporting a solid particle adhering to a flexible member.

The prior art has been identified as US3566677. It describes an apparatus for transporting droplets of liquid formed in a reservoir ('assembly 1') using a flexible member 3 made of interconnected loops 18 disposed for receiving the droplets from reservoir 1, the droplets adhering to loops 18 of the flexible member 3 by virtue of the surface tension of the liquid and being transported to an analyser. Claim 1 of the present application is not novel compared to that prior art. The use of a fiber (claims 2-3) or a ribbon (claim 4) as a flexible member for transporting droplets adhering by virtue of the surface tension of the liquid is also known. See for the use of fibers EP641599 (page 6 lines 34-43) or EP286410 (page 2, lines 11-16) and for the use of ribbons US5334837 (figure 27).

1. When compared to that prior art, the special technical features of group 1 in the sense of Rule 13.2 PCT is that the flexible member is formed into an enclosure for encapsulating at least one droplet of the liquid (claim 5), or that the flexible member is wrapped onto a drum having a plurality of wells within its surface, the droplets being positioned in each well. The problem to be solved is not to perturb the integrity of the droplets (see description page 11 lines 5-9 or page 12 lines 16-21)

2. When compared to the same prior art, the special technical feature of the second set of claims would be that the flexible member has compound selective wetting characteristics. The problem to be solved could be to control the chemical composition of the droplets (desc. page 8, line 9).

3. When compared to the same prior art, the special technical feature of the third set of claims would be the use of means for translating droplets. The problem to be solved is to move the droplets relative to the flexible member (desc. page 10, lines 13-14)

4. When compared to the same prior art, the special technical feature of the fourth set of claims would be the use of flexible members for mixing droplets. The problem to be solved is to combine droplets (desc. page 7, lines 11-24)

5. When compared to the same prior art, the special technical feature of the fifth set of claims would be the use of means for measuring the position of the droplets. The problem to be solved is to track the variation in position due to lengthening or shortening of the flexible member (page 8 lines 13-15)

6. When compared to the same prior art, the special technical feature of the sixth set of claims would be the use of a flexible member for transporting solid particles adhering by virtue of electrostatic force. The problem to be solved is the transport of solid particles (see desc. page 6 lines 27-30).

The above analysis shows that the special technical features of the different groups of claims are neither the same nor corresponding. The problems solved are different and do not form a single inventive concept in the sense of Rule 13.1 PCT.

This ISA considers therefore that this application do not fulfill the requirement of unity of invention and comprises six different claimed inventions.

INTERNATIONAL SEARCH REPORT

Information on patent family members

In International Application No

PCT/US 98/17306

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 98/17306

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